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TITLE: A Phase I Trial of an Immune Checkpoint Inhibitor Plus Stereotactic Ablative Radiotherapy in Patients with Inoperable Stage I Non-Small Cell Lung Cancer

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13. SUPPLEMENTARY NOTES					
14. ABSTRACT This clinical trial is the first to evaluate the synergy between radiation, a well-known immune modulator, with the novel immune checkpoint inhibitor MPDL3280A (atezolizumab) in early stage inoperable non-small cell lung cancer. The trial is comprised of a traditional 3 + 3 phase I design followed by a dose expansion. We have enrolled 3 patients into dose level 1. Two patients have completed the entire treatment plan and 1 patient is in the 9-week dose limiting time period. The regimen has been well tolerated with no dose limiting toxicities observed in the first two patients. One patient had a partial response and the other patient has stable disease. Interestingly patient #1 had tumor shrinkage after two cycles of low dose MPDL3280A without the radiation. The trial continues as planned.					
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1. INTRODUCTION:

Patients with inoperable stage I non-small cell lung cancer are treated with stereotactic ablative radiotherapy (SAR), which is a precise, highly focused radiation technique. Unfortunately, patients with inoperable disease who have been treated with SAR develop recurrences, including the spread of the tumor to new areas of the body (metastases). The chemotherapy often employed to reduce the risk of metastases is not offered to patients with inoperable disease for fear of side effects. As a result, 30% of such patients will die from metastases within 3 years. A new class of drugs called immune checkpoint inhibitors exploit the body's immune system to target and kill tumor cells. The drug used in the proposed trial, MPDL3280A (atezolizumab), blocks signals on tumor cells that allow them to evade the immune system. This study will test whether atezolizumab can be combined with SAR to safely improve outcome. The rationale for this combination is based on the idea that radiation therapy, a well-known mediator of the immune response will partner with the immune checkpoint inhibitor to enhance the body's immune response against tumor cells and promote tumor cell death. The proposed clinical/translational trial seeks to provide the first human evidence for combining SAR with an immune checkpoint inhibitor, with the goal of eradicating subclinical metastatic disease and increase the cure rate for early stage lung cancer in patients who cannot tolerate surgery.

2. KEYWORDS:

Stage I inoperable non-small cell lung cancer, stereotactic ablative radiotherapy, immunotherapy, immune checkpoint inhibitors, MPDL3280A and atezolizumab.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: To conduct a phase I clinical trial of the combination of MPDL3280A plus SAR.

Specific Aim 2: To assess the biological changes of MPDL3280A plus SAR in patient specimens, will not begin until completion of Specific Aim 1.

What was accomplished under these goals?

Specific Aim 1: We have completed Major Tasks 1 and 2 (write the clinical protocol/metric 2 months and completed prior to grant start date of 9/30/15 and navigate the study activation process/metric 2-5 months and completed prior to the grant start date). We are currently working on Major Task 3 which is enrolling into the dose finding phase of the study planned (metric 5-20 months). Sixteen patients have been prescreened, 14 from UC Davis (UCD) and 2 from David Grant Medical Center (DGMCC). Of these 14, three patients were consented and enrolled in the first dose level. Two patients have completed all therapy and no dose limiting toxicities (DLTs) were seen. Patient 1 had a minor response to MPDL3280A after 2 cycles and a partial response (PR) after

completion of all treatment. This patient developed grade 1 generalized edema and grade 1 leukopenia that might possibly be related to MPDL3280A. The 2nd patient did not experience any DLTs and had stable disease at the end of treatment. This patient had a transient grade 1 lymphopenia, hyponatremia and hypokalemia that might possibly be related to treatment. The third patient was delayed in starting treatment for one month due to a dental procedure. She is currently in week 1 of the 9 week DLT period. No additional patients can be accrued until this patient completes the DLT period.

Due to the slower than expected accrual our radiation colleagues at Mercy Medical Center in Sacramento have agreed to assist us by referring patients to us while providing standard of care radiation therapy at their site. IRB approval for this change has been granted. This modification has been submitted to the HRPO for approval.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to the communities of interest?

Nothing to Report

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Not applicable

Actual or anticipated problems or delays and actions or plans to resolve them

Due to the slower than expected accrual our radiation colleagues at Mercy Medical Center in Sacramento have agreed to assist us by referring patients to us while providing standard of care radiation therapy at their site. UCD IRB approval for this change has been granted. This modification was submitted to the HRPO for approval on 10/26/16.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Not applicable

Significant changes in use or care of human subjects

Not applicable

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

Publications, conference papers, and presentations

Nothing to Report

Website(s) or other Internet site(s)

Nothing to Report

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the projects?

Name:	Karen Kelly, MD
Project Role:	Principal Investigator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	4
Contribution to Project:	Dr. Kelly has written the protocol, informed consent and developed the case report form and seen these through the scientific, regulatory and contracting processes. Dr. Kelly has conducted the site initiation visit and activated the protocol and is actively recruiting patients for the study. Dr. Kelly has enrolled two patients onto the study.
Funding Support:	N/A
Name:	Megan Daly, MD
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID)	Unknown.
Nearest person month worked:	3
Contribution to Project:	Dr. Daly is actively recruiting patients for the study. Dr. Daly has enrolled one patient onto the study.
Funding Support:	N/A
Name:	Arta Monjazez, MD, PhD
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	3
Contribution to Project:	Dr. Monjazez is actively recruiting patients for the study.
Funding Support:	N/A
Name:	Lt. Col. James Mitchell, MD
Project Role:	Co-Investigator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	3
Contribution to Project:	Dr. Mitchell is actively recruiting patients for the study.
Funding Support:	N/A
Name:	Frances Lara, CRC
Project Role:	Clinical Research Coordinator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	3
Contribution to Project:	Ms. Lara assists the investigators in coordinating the screening of patients for the study and maintains this information for the grant. Ms. Lara processes the consent forms for enrolled patients. Ms. Lara monitors the patient's status.
Funding Support:	N/A
Name:	Laura Brennan, NP
Project Role:	Nurse Practitioner
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	2
Contribution to Project:	Ms. Brennan provides symptom and toxicity management and documentation of toxicities for clinical trial patients.
Funding Support:	N/A

Name:	Nichole Mahaffey, PhD
Project Role:	Data Coordinator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	1
Contribution to Project:	Ms. Mahaffey is responsible for patient registration, confirmation of patient eligibility, and entry of all patient data to the Velos study database for enrolled patients
Funding Support:	N/A
Name:	Leigh Anne Morris
Project Role:	Regulatory Coordinator
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	1
Contribution to Project:	Ms. Morris maintains all regulatory documents, prepares and submits protocol and informed consent form amendments, renewals and responses to the IRB, performs SAE reporting, IND submission and reporting and submission of necessary documents to HRPO.
Funding Support:	N/A
Name:	Pawandeep Aujla, PhD
Project Role:	Quality Assurance Manager
Research Identifier (e.g. ORCID ID)	Unknown
Nearest person month worked:	1
Contribution to Project:	Ms. Aujla is responsible for conduct reviews of clinical research records for data integrity and clinical research compliance. She will report any and all discrepancies to the Principal Investigator, establish a corrective action plan where appropriate, and perform training and follow-up with study personnel when any deficiencies are discovered.
Funding Support:	N/A

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Not Applicable

9. APPENDICES

Not Applicable